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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,329	03/31/2004	Arlindo L. Castelhano	60390-AZ-PCT-US/JPW/GJG/J	9147

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EXAMINER	
MOORE, SUSANNA	
ART UNIT	PAPER NUMBER
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,329	CASTELHANO ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,11.12,19,22,23 and 187-189* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11.12,19,22,23 and 187-189* is/are allowed.

6)☒ Claim(s) *5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Applicant's argument, see Remarks, refiled 1/26/2007, with respect to the Non-Final Office Action mailed 5/17/2005 have been fully considered. The following rejections are pending rejections or are necessitated by Applicants amendments. Claims 5, 11, 12, 23, and 187-189 are pending in the Application.

Specification

The abstract of the disclosure is objected to because the abstract is too short and generic. Correction is required. See MPEP § 608.01(b). Applicants state an amended abstract was submitted with the preliminary amendments but both abstracts on file are identical. The Examiner suggests resubmitting the amended abstract.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "neutrophil chemotaxis" is not a disease. This term refers to the body's natural process that occurs as a first line of defense against an infection or inflammation.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "sedation" is not a disease. Sedation is a state that is produced by pharmaceuticals.

Applicant is enabled for the treatment of antidiuresis, glaucoma, mast cell degranulation, asthma, allergic rhinitis, bronchitis and bronchoconstriction.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled. .

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. Owing to the range of 5 primary variables, thousands of pyrrolo[2,3-d]pyrimidine compounds are embraced.

(b) Scope of the diseases covered. Claim 5 is drawn to a method for treating a disease or condition associated with increased levels of adenosine, wherein the disease or condition associated with increased levels of adenosine in the subject is neutrophil chemotaxis, Parkinson's disease, sedation, cerebral ischemia or chronic obstructive pulmonary disease. The scope is unknown because "neutrophil chemotaxis" is not a disorder. This is a normal body process that occurs as a first line of defense against an infection or inflammation. Also, sedation is a state, which is not treated, but is produced by pharmaceuticals.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli.

Cerebral ischemia is an ischemic condition where the brain or parts of the brain do not receive enough blood flow to maintain normal neurological function. Cerebral ischemia can be the result of various diseases, or the result of arterial obstruction such as strangulation. This is typically secondary to stroke, injury, or cardiac arrest due to heart attack.

The claims also cover a method for the treatment of antidiuresis, glaucoma, mast cell degranulation, asthma, allergic rhinitis, bronchitis and bronchoconstriction but these are deemed enabled.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information 0.2-140 mg/kg per day is stated at the bottom of page 39. Moreover, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for all the diseases listed under the Scope of diseases above.

(D) State of the Prior Art: These compounds are substituted pyrrolo[2,3-d]pyrimidines with a particular substation pattern. So far as the examiner is aware, no pyrrolo[2,3-d]pyrimidines of any kind have been used for the treatment of any or all the diseases listed under the Scope of diseases above as not enabled.

(E) Working Examples: There is an in vitro assay, drawn to binding to a human A1 receptor expressed in yeast, described in lines 9-22, page 105 with data on compound CDS-116676 only. There is an in vitro assay, drawn to binding to a human A2a receptor expressed in yeast, described in the passage spanning line 24, page 105 to line 4, page 106 with data on compound CDS-116676 only. There is an in vitro assay, drawn to binding to a human A2b receptor

expressed in yeast, described in the passage spanning line 26, page 106 to line 16, page 107 with data on compound CDS-116676 only. There is an in vitro assay, drawn to binding to a human A3 receptor expressed in yeast, compound CDS-116676 only. There is an in vitro assay, drawn to binding to a human A3 receptor expressed in yeast, described in lines 6-24, page 106 with data on compound CDS-116676 only. There is data on compounds found in pages 109- 124. Of all these compounds only one, CDS-116676, on page 122 fits the limitations of the present formula I. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to clinical efficacy for the treatment of any of the claimed diseases. Although Applicants have established that this compound binds to the four receptors, they have not established if the compound is an agonist or an antagonist at any or all of these receptors.

(F) Skill of those in the art: The diseases listed under the Scope of diseases above are all different diseases and disorders that occur in different parts of the body and by different mechanisms of action.

Baraldi (Expert Opinion on Therapeutic Patents, 2004) states, in the first complete paragraph, page 77, in his conclusion that A1 agents "efficacy has yet to be shown." Baraldi (Expert Opinion on Therapeutic Patents, 1999) states, in the final paragraph, on page 524, "[t]he different effects of A3 receptor agonists in vitro and in vivo are still not clear".

The skill level depends on the disease. For example, there is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function.

Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Moreover, currently there is no treatment for Parkinson's disease itself, only the symptoms as a result of the disease are treated with L-DOPA, inhibitors of the enzyme COMT, Selegiline, dopamine agonists, anticholinergics and amantadine.

(G) The quantity of experimentation needed: Owing especially to factors A, D, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Applicant's traverse the above enablement rejection setting forth five main issues: 1) the lack of any correlation between clinical efficacy for treatment of the twelve diseases and Applicants, four in vitro assay; 2) the limited biological testing done upon compounds within the scope of formula (I); 3) the state of the prior art; the complete lack of skill of clinicians in using A1 agonists in treating disease; and 5) the breadth of the claims.

Applicant addressed points 1 and 2 above together. Applicants argue the first two points by citing *Cross v Iizuka*, "a rigorous or invariable exact correlation is not required." A rigorous

correlation was not required although the M.P.E.P. does state, "The initial burden is on the examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example." The Examiner has satisfied this burden in discussing the Baraldi reference. The compounds in the reference have the same mode of action, e.g. through the adenosine, and Baraldi noted the in vitro data did not correlate with the in vivo data. That is reason enough to question the correlation.

Secondly, Applicants state, "Data from the radioligand binding assay is an accepted means to correlate a compound to its use. See, e.g. Section 1.3 entitled In vitro Test Systems of Yan, Exper Opinion on Emerging Drugs, which states that:
[Adenosine receptors] and their ligands may be investigated in binding and functional assays. Radioligand binding assays can be conducted easily and fast; the data directly reflect the interaction of a compound with the receptor protein without uncontrollable intermediate steps."

This statement only mentions the interaction between the compound with the receptor. The cited section does not provide any support for the correlation between the in vitro binding and in vivo assays for the treatment of diseases, which is the issue at hand.

Next the references will be addressed.

1. Marx, D. et. al., Drugs News Perspect. (2001). Applicant is enabled for most of the diseases mentioned in this reference, except neutrophil chemotaxis. As mentioned above, this is a normal body process, not a disease.

2. Knutsen et. al., Current Opinion in Invest. Drugs (2001). This reference provides an adenosine receptor antagonist KW-6002 for the treatment of Parkinson's disease, which is in

Phase II clinical trials. The skill level is very low relative to the difficulty of task. Parkinson's Disease is a neurodegenerative disorder, which, like most neurodegenerative disorders, has been highly resistant to pharmaceutical treatment. The disorder is characterized by a deficiency of dopamine. This deficiency arises from the degeneration and death of dopamine-preducing cells in the substantia nigra, located in the midbrain, along with the presence of cytoplasmic protein inclusions called Lewy bodies. PD is considered to be a cluster of related disorders. The majority of cases of PD are deemed sporadic, but there are also familial forms of PD. This death is of unknown origin (idiopathic), and cannot itself be stopped. Current drug regimens for Parkinson's disease are aimed instead at symptomatic relief, primarily through a dopaminergic effect. This includes dopamine replacement therapy (L-dopa), COMT inhibitors (which facilitate the conversion of L-Dopa to dopamine itself, Amantadine (which appears to increase dopamine synthesis), dopamine agonists (which mimic dopamine) or MAO B inhibitors (e.g. Selegeline, which reduces or delays the breakdown of dopamine). These do not actually treat the disease itself, but instead seek to boost the amount of dopamine available by various mechanisms. At the time of filing, and indeed at present, no drug has been scientifically demonstrated to treat the disease itself, rather than provide relief for this or that symptom. Medications used to treat the symptoms of Parkinson's disease cannot step the disease from progressing over time. It is true that Interleukin (IL)-1 beta, IL-2, IL4, IL6 and transforming growth factor alpha levels are elevated in Parkinson's disease patients, as well as some other chemicals. For reasons set forth above, this does not mean that there is any reasonable expectation of treatment success. This is simply a biological observation, whose meaning is unknown.

With regard to KW-6002 (istradefylline), this drug a) has not been established as

effective and b) is not a treatment for PD per se, but rather for motor complications of PD (i.e. relief of symptoms).

3. Szkotak A. J. et. al., Am. J. Physiol. Cell Physiol. (2001). Applicant states this reference describes the affects of adenosine receptor on respiratory epithelial cells. While Applicant is enabled for asthma, Applicant is not enabled for COPD. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

4. Phillis, J.W., Brain Research (1995). Applicants states this the reference provides support for prevention of cerebral injuries, i.e. cerebral ischemia. As indicated above under the Scope of diseases, cerebral ischemia can be the result of various diseases, e.g. tumor, or the result of arterial obstruction, such as strangulation. This old reference states in the last line of the abstract, "These results suggest that adenosine A2A receptor antagonists may be useful for the prevention of cerebral injuries resulting from stroke or cardiac arrest." The words "may" and "suggest" are not definitive. If something is merely suggestive it is not yet enabled.

5. Welch, W. J., Expert Opn. Investig. Drugs (2002) and 6. Avila, M.Y. et. al., Br. J. Pharmacol. (2001) are directed to the use as a diuretic agent and the treatment of glaucoma, which are deemed enabled.

Next, points 3 and 4 will be addressed. Applicants contend that the Examiner misrepresents Yan's (2001) reference. Applicants cite several statements, which are provided below:

"Partial [Al-selective] agonists may be advantageous, especially for non-cardiovascular indications, and are currently in preclinical development.

A2a agonists are anti-inflammatory agents.

A3-selective agonists have been described as promising cardio- and cerebral protective agents."

The "may" and "promise" are not evidence of enablement but in fact point against it. A promise is not definite; it's a hope of something to come, which may or may not happen. Furthermore, Applicants compounds are not believed to be agonists.

Applicants also point out the following statements contradict the statements the Examiner used from the Baraldi reference.

"By regulating cell death, A3 receptors could play a fundamental role in human disease. This relationship between A3 receptor and apoptosis suggests that A3 ligands could be useful in the

treatment of diseases in which cytoxicity is undesirable, such as neurodegenera~ive disorders, cancer, inflammation, asthma, etc." (pg. 525)

"Furthermore, selective activation of A3 receptors appears to inhibit human neutrophil degranulation, suggesting the anti-inflammatory potential of A3 agonists in neutrophil-mediated tissue injury (pg. 525)."

Here again, the words "could" and "suggests" are not definitive. If something is merely a prospect it is not yet enabled.

In the last point 5, Applicant asserts the scope of the claims is not broad because "the genus is sufficiently described by a representative number of species and sufficient to shoe the Applicants were in possession of the claimed genus." This does not address the fact that the scope of the compounds is exceptionally broad. This statement actually supports a written description rejection, which is not the issue at hand. The issue at hand is the above enablement rejection.

Regarding the obviousness-type double patenting, the terminal disclaimer has been received and approved.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SM

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